# Proposed Decision Memo for Extracorporeal Photopheresis (ECP) (CAG-00324R2)

## Decision Summary

CMS proposes coverage for ECP for this indication only when ECP is provided under a clinical research study that meets the following conditions.

The clinical research study meets the requirements specified below to assess the effect of ECP for the treatment of BOS following lung allograft transplantation. The clinical study must address one or more aspects of the following question:

Prospectively, do Medicare beneficiaries who have received lung allografts, developed BOS refractory to standard immunosuppressive therapy, and received ECP, experience improved patient-centered health outcomes as indicated by:

a. improved forced expiratory volume in one second (FEV1);
b. improved survival after transplant; and/or
c. improved quality of life?

We note for the sake of clarification of terms that certain sections of this document refer to an existing international classification of the severity of BOS, the 2002 International Society for Heart and Lung Transplantation (ISHLT) definition of BOS (please see table, p. 5). In one area below, we refer to an earlier (1993) version of this classification used by the Villanueva 2000 study (please see p. 12 below), one clinical study germane to this decision.

This decision would not modify existing requirements for any other covered or non-covered indication for ECP (Section 110.4 Medicare National Coverage Determinations Manual).

The required clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether ECP potentially improves the participants' health outcomes.
b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR parts 50 and 56.
g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors

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l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

CMS further proposes that any applications for coverage of ECP in CED studies for this indication pursuant to this NCD must be received and approved by May 2, 2014. If there are no approved clinical studies on this date, this NCD will expire and coverage of ECP for BOS will revert to the coverage policy in effect prior to the issuance of the final DM for this NCD.

In order to maintain an open and transparent process, we are seeking comments on our proposal. We will respond to public comments in a final decision memorandum, consistent with the spirit of §1862(l) (3) of the Act.

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## Proposed Decision Memo

TO: Administrative File: CAG-00324R2

Extracorporeal Photopheresis (ECP)

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SUBJECT: Proposed Decision Memorandum for CAG-00324R Extracorporeal Photopheresis (ECP)

DATE: February 2, 2012

## I. Proposed Decision

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## II. Background

### A. Extracorporeal photopheresis (ECP)

ECP is a medical procedure in which a patient's white blood cells are exposed first to the drug 8-methoxypsoralen (8-MOP) and then to ultraviolet A (UVA) light. The procedure starts with the removal of the patient's blood, which is centrifuged to isolate the white blood cells. The drug is typically added to the white blood cells after they have been removed from the patient (referred to as *ex vivo* administration) but the drug can alternatively be administered to the patient before the white blood cells are withdrawn. After UVA light exposure, the treated white blood cells are re-infused into the patient.

ECP is usually performed on two consecutive days at four-week intervals with clinical evaluation at six months to determine response. The duration of treatment varies significantly depending on the medical condition being treated, and the patient's response to the treatments.

ECP is frequently administered via the UVAR® XTS™ system, an FDA-approved automated apheresis and processing system. This system collects a patient's blood, isolates the white blood cells, adds 8-MOP and irradiates the treated white blood cells with UVA. Other systems and protocols have been used to administer ECP. In this decision memorandum as in previous ones, CMS is evaluating ECP as a procedure, and not a specific system for administering ECP.

The exact mechanism of action of ECP on the immune system is still unclear. It is thought that when activated, 8-MOP molecules bind with the DNA of the white blood cells, which kills the cells. The dead white blood cells, once reinfused into the patient, stimulate multiple different cells and proteins of the patient's immune system in a series of cascading reactions. This activation of the immune system then impacts the illness being treated. The precise manner in which chronic rejection of a lung allograft is affected by ECP is unknown.

**B. Bronchiolitis Obliterans Syndrome (BOS) Following Lung Allograft Transplantation**

BOS was described in 1984 in a small series of transplant recipients who developed progressive decline in lung function of non-infectious cause, beginning several months to a few years after heart-lung transplantation (Burke 1984). BOS refers to progressive decline in respiratory function. Its relation to chronic rejection and long-term failure survival of lung allografts stimulated a number of efforts to improve the immunosuppressive regimen for transplant patients in the 1990's. However, BOS is estimated to be present in more than 50% of lung allograft recipients at five years after transplantation, and remains a major obstacle to long-term lung transplant survival (Belperio 2009).

Clinically, BOS has an insidious onset with progressive exertional dyspnea, often accompanied by cough. Sometimes a bronchial infection seems to trigger its onset, with acute dyspnea, wheezing and the development of obstruction. Later in the course of the disease, superinfections and bacterial or fungal colonization are common. At that time, CT scan of the thorax often reveals bronchiectasis and other signs of chronic infection. Once established, untreated BOS may develop progressively and lead to severe obstruction with respiratory insufficiency and death resulting from an infectious exacerbation. Sometimes, episodes of progressive loss of lung function alternate with stable intervals. (Verleden 2005)

The histologic diagnosis of obliterative bronchiolitis (OB), a manifestation of chronic lung allograft rejection, depends on recognizing a pattern of progressive damage to the small airways. The sequence of pathologic changes in OB includes development of lymphocytic bronchiolitis; epithelial damage and ulceration; proliferation of fibroblasts and intraluminal granulation tissue; and ultimately fibrosis and scarring of small, non-cartilaginous bronchioles (Belperio 2009). Advanced disease can culminate in total obstruction and fibrotic obliteration of bronchioles. The patchy nature of OB, particularly in its early stages, has frustrated monitoring efforts after transplantation due to the relative insensitivity of serial biopsies to detect OB (Verleden 2005).

Because a reliable sign of BOS was unavailable from histopathologic examination of serial biopsies for OB, a consensus definition emerged (Belperio 2009) in which the diagnosis of BOS was defined by a sustained ( greater than 3 weeks) decline in expiratory flow rates, provided that alternative causes of pulmonary dysfunction have been excluded. International efforts (published first in 1993 and then revised in 2002) by professional societies such as ISHLT defined BOS clinically, in terms of forced expiratory volume in one second (FEV1), reflecting the persistent airflow obstruction seen in chronic allograft rejection (Estenne 2002). The 2002 ISHLT definition of BOS severity is shown in the following table. Note that, within each BOS severity category below, subtypes ‘a’ and ‘b’ exist, based on either no pathological evidence of OB or no pathological material for evaluation (‘a’) or pathological evidence of OB (‘b’).

Table: ISHLT 2002 Definition of BOS Severity

| BOS Category | FEV1 as % of baseline* |
|---|---|
| BOS 0 | > 90% |

| | |
|---|---|
| BOS 0-p | 81% to 90% |
| BOS 1 | 66% to 80% |
| BOS 2 | 51% to 65% |
| BOS 3 | 50% or less |

* - ‘Baseline’ is defined as (Estenne 2002) “the average of the 2 highest (not necessarily consecutive) measurements obtained at least 3 weeks apart, obtained without the use of an inhaled bronchodilator preceding the study”.

Although BOS is rare within the first year after lung transplantation, the cumulative incidence of BOS ranges from 43 to 80% within five years of transplantation. Data from the ISHLT registry, representing more than 10,000 transplants followed from April 1994 through June 2006, showed that 25% had developed BOS by 2.5 years, and 50% by 5.6 years.

Survival after development of BOS varies by rapidity of decline of pulmonary function: in one study, those with more rapid decline survived a median of 29 months, while those with slower decline survived a median of 58 months (Belperio 2009). Worsening BOS grade (from 1 to 2 or from 2 to 3) is associated with higher mortality (Burton 2007). Other studies have reviewed the role of inflammation and repair in the development of BOS in lung allograft recipients. The complex balance of factors including host immune reaction to foreign tissue; airway infection; ischemia; other host factors including gastroesophageal reflux; and potentially a localized graft-versus-host reaction by surviving donor lymphocytes interacting with recipient antigens has been summarized (Belperio 2009).

Because a specific cause of BOS is not yet known, various approaches have been proposed for its prevention or control (other than ECP, the topic of this NCD reconsideration). These include improved immunosuppression following transplantation; better histocompatibility matching of recipients to donor lungs; use of broad-spectrum antibiotics, such as azithromycin to reduce BOS risk; more effective anti-lymphocyte therapies and combination regimens; and improved allograft screening for infectious potential. (For example, Vos 2011)

## III. History of Medicare Coverage

In April 1998, CMS issued a national coverage determination (NCD) for ECP providing coverage by Medicare only when used in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that has not responded to other therapy.

In December 2006, CMS issued a reconsideration of its 1998 NCD that determined that extracorporeal photopheresis is reasonable and necessary for patients with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment; and patients with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment. CMS also determined that ECP is not reasonable and necessary for the treatment of bullous pemphigoid and pemphigus vulgaris.

All other indications for extracorporeal photopheresis remain non-covered.

### A. Current Request

The Centers for Medicare & Medicaid Services (CMS) received a formal written request for reconsideration to add coverage for ECP treatment for patients who have received lung allografts and then developed progressive bronchiolitis obliterans syndrome (BOS) refractory to immunosuppressive drug treatment. The request was submitted by Doctors RR Hachem and GJ Despotis, both of the Washington University in Saint Louis School of Medicine, and KE Berman of Health Research Associates (referred to as 'the NCD requesters').

## B. Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage §1812 (Scope of Part A); §1832 (Scope of Part B) and §1861(s) (Definition of Medical and Other Health Services) of the Act. ECP is considered to be within the following benefit category: 1861(s) (1) (physician services).

## IV. Timeline of Recent Activities

| | |
|---|---|
| August 4, 2011 | CMS accepts the formal request for reconsideration to add coverage for ECP treatment for patients who have received lung allografts and then developed progressive bronchiolitis obliterans syndrome (BOS) refractory to immunosuppressive drug treatment. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced. |
| September 3, 2011 | The initial 30 day public comment period ended. 22 timely comments were received. |
| | Proposed decision posted |

**V. FDA Status**

In April 1987, the FDA approved (docket number 87M-0136) the application of Therakos, Inc. (Johnson and Johnson) for pre-market approval of the UVAR Photopheresis System. (Source: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/PMA.cfm?id=16433)

In August 1999, the FDA approved the Therakos UVAR XTS system (PMA #P860003/S31). While this is an upgrade to the original device, the fundamental technology, function and intended use has not changed. (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=8758)

In 1999, the FDA approved UVADEX® (methoxsalen) Sterile Solution, which is indicated for extracorporeal administration with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment. (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=18471 )

In March 2009, the FDA approved the Therakos CELLEX system (PMA #P860003/S48). While this is an upgrade to the original device, the fundamental technology, function and intended use has not changed. (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?start_search=1&applicant=&tradename=&productcode=LNR&pmanumber=p&advisorycommittee=&docketnumber=&supplementtype=&expeditedreview=&ivdproducts=off&decisiondatefrom=1/1/2009&decisiondateto=1/1/2010&noticedatefrom=&noticedateto=&so)

## VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

## VII. Evidence

### A. Introduction

This section provides a summary of the evidence that CMS considered during the review. No randomized controlled clinical trials were found that investigated the use of ECP in lung allograft recipients with BOS refractory to immunosuppressive drug therapy. The evidence reviewed for this decision memorandum, therefore, consists of results from uncontrolled clinical trials and from case studies published as full length literature article.

### B. Discussion of Evidence Reviewed

#### 1. Question and Outcomes

Prospectively, do Medicare beneficiaries who have received lung allografts, developed BOS refractory to standard immunosuppressive therapy, and received ECP, experience improved patient-centered health outcomes as indicated by:

a. improved forced expiratory volume in one second (FEV1);
b. improved survival after transplant; and/or
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The goal of ECP therapy is to eliminate the immunological attack on the lungs, especially on the bronchioles. In the absence of more direct measures, such as serial biopsies of the bronchioles, the primary outcome measured in clinical studies and case studies reviewed was progression of BOS, measured as the change in rate of decline in $FEV_1$.

CMS prefers evidence about health outcomes actually experienced by the patient, such as survival after transplant. Another patient-centered health outcome is quality of life. Additionally, a decrease in disease activity due to ECP, even if it is less than a total resolution of disease activity, may reduce the patient's need for immunosuppressive drug doses and thereby lessen the risk of infection.

**2. External Technology Assessments**

CMS did not request an external technology assessment (TA) on this issue.

**3. Internal technology assessment**

The reviewed evidence was gathered from articles submitted by the NCD requesters and from a literature search of the PubMed database by CMS staff.

The NCD requesters provided the full text of 47 articles they considered relevant to the requested reconsideration. Of the 47 submitted articles, 16/47 were review articles or professional society consensus statements, and one of 47 was a letter to the editor. Of the remaining 30/47 articles, 25 were clinical studies on topics unrelated to the specific research question for this NCD reconsideration. Of the remaining five of 47 articles, three were clinical studies with fewer than ten human lung allograft recipients with BOS refractory to immunosuppressive drug therapy for which ECP was used as treatment. Two articles (Morrell 2010 and Benden 2008) are summarized below. In addition, the requesters submitted a detailed public comment (see below under Section VII, 'Public Comments').

*Literature search methods*

In August 2011, CMS staff used the search terms "bronchiolitis obliterans syndrome" and "extracorporeal photopheresis" to find relevant articles.

CMS also reviewed all information submitted by the NCD requesters. The information they provided consisted of the 47 published articles of various types (noted above); and, received separately as a public comment, a summary and interpretation of a recent clinical study (Morrell 2010) for which two of the requesters were co-authors (Drs. Despotis and Hachem).

CMS also reviewed any references submitted with any public comments. Of eleven references from public comments:

one of eleven was a study of heart transplant recipients;
one of eleven described an experiment in mice;
one of eleven was a review article;
one of eleven was a letter to the editor with insufficient information for analysis;
one of eleven was a professional society guideline;
three of eleven were small case series with less than ten human subjects;
two of eleven were articles (Morrell 2010 and Benden 2008) summarized below; and
one of eleven (Villanueva 2000) was a case series of 14 patients that was reviewed in full-text form by CMS staff and is summarized below.

In its own literature search, CMS included clinical studies of ECP in human subjects with BOS not responding to immunosuppressive therapy, in which at least ten individuals participated, and in which sufficient data was provided to assess study design, execution, and findings. CMS did not identify any articles in addition to those provided by the NCD requesters or by public commenters. In addition, CMS staff found that the published medical literature on ECP for BOS did not include any systematic reviews or meta-analyses.

*Retrospective Case Series*

***Benden C, Speich R, Hofbauer GF, et al. ECP after lung transplantation: a ten year single-center experience. Transplantation 2008; 86(11): 1625-7.***

In this report, results of a retrospective case series from one transplant center are based on twelve lung transplant patients undergoing ECP for BOS refractory to aggressive immunosuppressant therapy. [CMS notes that this article also included results of ECP therapy for twelve other patients, none of whom developed BOS, who received ECP for recurrent acute rejection of the lung allograft. Results of ECP therapy for these twelve other patients are not summarized for this analysis.] Insufficient information was provided in the report to establish the ages, genders, types of transplants received (unilateral or bilateral lung), or underlying diagnoses leading to transplantation, of the twelve patients undergoing ECP for BOS. All twelve patients with ECP for BOS completed twelve two-day cycles of ECP. At the start of ECP therapy, five of these twelve patients had BOS 1; two of the twelve had BOS 2; and the remaining five had BOS 3. The change in rate of decline in FEV1 was the primary outcome measure; graft survival post-ECP was the secondary outcome measure. The authors reported that the mean rates of decline in FEV1 were 112 ml/month before ECP and 12 mL/month after ECP (n=12, P=0.011, 95% confidence interval (CI) for change in rate of decline: 28 – 171 mL/month). The authors also reported that there was no significant change after ECP in absolute values of FEV1. Among patients dying during the 10 year study period, the cause of death was BOS. No ECP-related adverse events were reported, among any study patients. The authors concluded that ECP reduces the rate of decline of lung function in lung transplant recipients with BOS and is well-tolerated. The authors mentioned that during the study, all patients were treated with a cyclosporine-A based immunosuppressant regimen.

***Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for BOS after lung transplantation. J Heart Lung Transplant 2010 Apr; 29 (4): 424-31.***

In this retrospective study, the authors analyzed the efficacy and safety of ECP for BOS at one institution. Between January 2000 and January 2007, 60 lung allograft recipients were treated with ECP for BOS. The participants included 32 men and 28 women, with median age (and range) of 58 (21-72) years. Primary diagnosis before transplantation included COPD (43%), CF (18%), idiopathic pulmonary fibrosis (15%), alpha-1-antitrypsin (A1AT) deficiency (13%), primary pulmonary hypertension (5%), and other (5%). Following transplantation, patients had been maintained on a triple drug immunosuppression regimen, with acute rejection episodes treated with steroids and documented based on followup bronchoscopies. BOS was diagnosed according to ISHLT standards. A 24-session ECP protocol was initiated when a progressive decline in a patient's lung function was refractory to cytolytic therapy with antithymocyte globulin, optimization of the drug immunosuppression regimen, and use of azithromycin. The outcome used was rate of decline (in milliliters (mL) per month) of FEV1 before and after ECP. Of the study group of 60 patients, four were excluded from further analysis due to death from respiratory failure before completing the entire ECP treatment protocol. For the other 56 patients studied, the mean rate of change in FEV1 during the 6 months before ECP initiation was -116.0 mL/month. During the 6 months period after ECP initiation, the mean rate of change in FEV1 was -28.9 mL/month. The mean difference in the rate of change in FEV1 from before to after ECP was 87.1 mL/month ($P < 0.0001$), 95% CI 57.3 – 116.9 mL/month). The authors evaluated the potential for length-time bias by excluding five patients (of 56) with BOS 1, but found that the mean difference in the rate of decline of FEV1 in 51 other patients (with BOS 2 and BOS 3) remained significant. In 14/56 patients, lung function improved, i.e., in these fourteen patients, FEV1 at 6 months after ECP increased by an average of 121 mL. Analysis of the response of the entire study group (n=51) during the extended period of twelve months after ECP demonstrated improvement of the mean difference in rate of change of FEV1 during the twelve months after ECP. The authors also investigated complications during treatment with ECP in all 60 patients. Eight patients were hospitalized for catheter-related sepsis. One of these eight patients died. No other complications were reported. The authors concluded that the differences from before ECP to both 6- and 12-month periods after ECP in rate of change of FEV1 seen in lung transplant recipients with BOS was significant, but they commented that limitations included the retrospective design of the study, the absence of a external control group, and the possibly confounding effect that ECP was used in conjunction with other immunosuppressive modalities that varied by individual patient. The authors suggested that further research would be appropriate.

***Villanueva J, Bhorade SM, Robinson JA, et al. Extracorporeal Photopheresis for the treatment of lung allograft rejection. Annals of Transplantation 2000; 5(3): 44-7.***

In this study of the use of ECP for the treatment of BOS, the authors retrospectively identified 14 patients which included three patients for clinical staging of BOS category 'a' and eleven patients who had biopsy proven OB. (CMS Note: this study used the 1993 ISHLT BOS severity category definitions (Cooper 1993).) Of these 14 patients, seven were female, and seven were male. The patients' mean age was 46 years. Seven of the 14 patients underwent bilateral lung transplantation; six underwent single lung transplantation, and one underwent heart lung transplantation. Primary diagnoses before transplantation included six patients with emphysema, five with cystic fibrosis, two with idiopathic pulmonary fibrosis, and one for pulmonary hypertension. All of the patients received standard immunosuppression with a three-drug regimen initially consisting of cyclosporine, azathioprine, and prednisone. Patients underwent ECP every two weeks for two months, and every month for two months, for a total of 6 treatments. FEV1 measurements were taken before and after ECP. Acute rejection episodes were treated with intravenous methylprednisolone, and some patients also received, antithymocyte globulin, total lymph node irradiation, and/or methotrexate for refractory rejection. The authors reported that at the time of diagnosis three patients were classified as BOS 0b; five as BOS 1, three as BOS 2, and three as BOS 3. In these 14 patients, time from transplantation to BOS development ranged from 7-51 months, with an average of 24 months. Eight of 14 patients were alive at the conclusion of the study. Mean (+/- SD) survival duration for all patients, after ECP therapy was 43 +/- 12 months, with mean survival of patients with BOS 2 or BOS 3 being 14 +/- 10 months. In six of 14 patients who died during the study period causes of death included BOS in four patients with BOS 2 or BOS 3, and lung cancer in two patients, one with BOS 1, and one with BOS 3. Among these six patients, deaths occurred from 6 – 34 months after ECP, with an average of 13 months after ECP. The authors noted no significant adverse events due to ECP treatment. The authors acknowledged that the small size and retrospective design of this study, the lack of randomized assignment of the treated group, and the absence of controls limited its generalizability. The authors concluded that ECP appears to be a promising therapy, especially for patients with less severe types of BOS.

*Additional retrospective case reports or small cases series:*

CMS was also informed of four additional publications describing small case series (n < 10) as summarized in the following table. These articles would not have been reviewed by CMS as sources of evidence given the inclusion criteria indicated above.

| Cited as: | Number of Participants | Notes: |
|---|---|---|

| | | |
|---|---|---|
| Meloni 2007 | 6 | Outcome studied: effect on CD4+ CD25+ Treg cells after ECP. |
| O'Hagan 1999 | 5 | Brief clinical report |
| Salerno 1999 | 8 | Outcome studied: subjective improvement. |
| Slovis 1995 | 3 | Brief case series (letter to the editor). Insufficient data for review. |

## 4. MEDCAC

A Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting was not convened on this issue.

## 5. Evidence-based guidelines

The American Society for Apheresis (ASFA) provided an evidence-based summary of ECP for treatment of BOS developing in lung allograft recipients. CMS did not find any other evidence-based guidelines relevant to this proposed decision.

***Szczepiorkowski ZM, Winters JL, Bandarenko N, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis. Journal of Clinical Apheresis 25:83–177 (2010)***

An evidence-based professional guideline from ASFA (Szczepiorkowski 2010) examined a variety of apheresis procedures, including ECP treatment for BOS developing in lung allograft recipients. ASFA considered BOS in lung allograft recipients to be a category II indication, that is, "(a) Disorder(s) for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment." On p. 126 of that article, a summary page with information about ECP for lung allograft rejection included the following.

> "… At first, ECP was used in the context of refractory BOS (Stages 2-3) in which beneficial effect was demonstrated by initial stabilization or improvement in FEV1. Since then, the literature suggested that ECP may be an effective therapeutic modality for stabilization of lung function in patients with persistent acute rejection and early BOS (Stages 0-p -1), thus preventing further loss of pulmonary function. As ECP is not likely to reverse fibroblast proliferation in the transplanted lung, earlier initiation of ECP may arrest BOS progression thereby inducing improvement in the patient's clinical status and FEV1. Two recent largest studies to date (60 and 24 patients) showed that ECP significantly reduced the rate of decline in lung function in transplant recipients with BOS in all stages as measured by FEV1. … Importantly, ECP is well tolerated and is not associated with an increased risk of infection, a common complication of immunosuppressant drugs." (Szczepiorkowski 2010, p. 126)

These authors gave ECP for BOS a category II assignment (Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.) They assessed the type of evidence for ECP for BOS as Type II-3, which they define as “Obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.” Their recommendation for ECP for BOS was Grade 1C, defined as “Strong recommendation, low-quality or very low-quality evidence” supported by observational studies or case series. They noted that, for Grade 1C recommendations, the recommendation could change if higher-quality evidence becomes available.

**6. Professional Society Position Statements**

Two professional societies expressed positions via submitted public comment.

The American Association of Blood Banks (AABB) stated that there currently is no other proven therapy other than ECP for lung allograft patients with BOS for whom standard immunosuppressive drug treatment has not been effective.

The American Society for Apheresis (ASFA) stated that ECP is a reasonable and clinically appropriate second line therapy to addressing lung allograft rejection. They acknowledge that most of the published data is limited to observational studies and to gather randomized clinical trial evidence on specific treatments of rare disorders is extremely difficult. (Please also see above summary of ASFA evidence-based assessment of ECP for BOS (Szczepiorkowski 2010).)

**7. Expert Opinion**

We may receive expert opinions on the proposed decision during the comment period.

## 8. Public Comments

*Initial Comment Period: August 4, 2011 – September 3, 2011*

CMS received 22 timely public comments during the first public comment period. All of the comments supported the request to add coverage for ECP treatment for patients who have received lung allografts and then developed progressive bronchiolitis obliterans syndrome (BOS) refractory to immunosuppressive drug treatment. Of these public comments received, thirteen/22 were from physicians, eight of whom specialize in lung transplantation, five/22 were from professors of medicine, two/22 were from professional societies, one/22 was from an individual who did not identify an associated organization or profession and one/22 was from the NCD requesters.

Of the 22 public comments, eleven contained one or more references, including in one case, references within a PowerPoint presentation sent with a comment. A review of the 11 unique published references showed that:

- Five of these eleven references provided no additional evidence relevant to the topic of this reconsideration: one was a study of heart transplant recipients; one described an experiment in mice; one was a review article; one was a letter to the editor with very brief descriptions of individual cases insufficient for analysis; and one (Szczepiorkowski 2010) was a professional society guideline which is summarized above under ‘Evidence -Based Guidelines”.

- Of the remaining six references, three of six were of minimal evidentiary value given the topic of the reconsideration request: one of these three was a chronological analysis of circulating immunologically active blood cells following ECP, but not of lung function; and two others of these three described small case series (O'Hagan 1999 (N=5), Salerno 1999 (N=8)) conducted in the 1990s.
- Among the remaining three references, two articles (Benden 2008 and Morrell 2010) were cited by the NCD requesters (and are summarized above in Section VII). One additional reference (Villanueva 2000), not submitted by the original requesters, was a case series that is also summarized above.

One public comment, submitted by the NCD requesters in their public comment on this reconsideration, provided a re-analysis of the Morrell 2010 article (for which two of the requesters were co-authors) focusing on the study's 25 Medicare patients, to determine whether Medicare beneficiaries specifically benefitted from ECP therapy. The re-analysis they provided is excerpted from their public comment below.

"Analysis of Medicare Sub-Cohort Treated With ECP Between 1/1/2000 – 12/31/2007

"In our previously published study,[1] regression slope values were calculated to develop a linear relationship between measured FEV1 values vs. time; these slope values reflect mean rates of change in FEV1 over time for all patients (n = 56) included in our analysis. Pursuant to interest expressed by CMS staff, we extended our analyses to examine the mean monthly rates of change in the Medicare (n = 25) and non-Medicare (n = 31) patient sub-cohorts. These rates of change were calculated for (1) the six-month period prior to initiation of ECP, (2) the six-month period following initiation of ECP, and (3) the 12-month period following initiation of ECP. Comparisons of mean monthly rates of decline in FEV1 prior to ECP versus six-month and 12-month post-ECP appear in Tables 1 and 2 below.

"As presented in Table 1 below, the mean rate of decline in FEV1 during the 6-month period before the initiation of ECP in the Medicare sub-cohort was -98.7 mL/month. The mean decrement in FEV1 during this 6-month period was 594 mL. During the 6-month period after the initiation of ECP, the mean rate of decline decreased to -31.9 mL/month. The mean decline in FEV1 during the 6 months after ECP initiation was 192 mL. The mean difference in the rate of decline of FEV1 was 66.8 mL/month (95% confidence interval [CI], 22.0 – 111.4 mL/month; $p < 0.005$).

"Table 1. Mean monthly rates of decline in FEV1, pre-ECP and 6 months post-ECP

| Group | 6 months prior to ECP (mL) | 6 months post-ECP (mL) | *p*-value | Mean difference (mL) (95% CI) |
|---|---|---|---|---|
| Medicare (n=25) | - 98.7 | - 31.9 | 0.005 | 66.8 (22.2 - 111.4) |
| Non-Medicare (n=31) | - 129.9 | - 26.4 | <0.0001 | 103.4 (62.1 - 144.8) |
| All Patients (n=56) | -116.0 | - 28.9 | <0.0001 | 87.1 (57.3 - 116.9) |

“The analysis was extended to twelve month after the initiation of ECP to evaluate the durability of the response; these findings are presented in Table 2 below. In the Medicare sub-cohort, the mean rate of decline over the twelve months following initiation of ECP was -24.3 mL/month, and the mean decrement in FEV1 during this 12-month period was 144 mL. The mean difference in the rate of decline between this 12-month period and the period before ECP was 74.4 mL (95% CI, 30.9 – 117.9 mL/month; $p$ = 0.002).

“Table 2. Mean monthly rates of decline in FEV1, pre-ECP and twelve months post-ECP

| Group | 6 months prior to ECP (mL) | 12 months post-ECP (mL) | *p*-value | Mean difference (mL) (95% CI) |
|---|---|---|---|---|
| Medicare (n=25) | - 98.7 | -24.3 | 0.002 | 74.4 (30.9 - 117.9) |
| Non-Medicare (n=31) | - 129.9 | -19.1 | <0.0001 | 110.8 (73.0 - 148.7) |
| All Patients (n=56) | -116.0 | -21.4 | <0.0001 | 94.6 (66.5 - 122.6) |

The NCD requesters also noted in their public comment that in a search of the national registry of clinical trials (clinicaltrials.gov), they identified two trials involving treatment of BOS in lung transplantation recipients. Finally, they noted that changes in pulmonary function after ECP treatment, as measured by changes in rate of FEV1 decline, was the sole primary outcome measure in these two trials.

They also noted that “We could not identify any controlled or single assignment clinical trials, evaluating any intervention to treat established BOS in lung transplantation patients that specified mortality as a primary outcome measure in the medical literature or in the ClinicalTrials.gov database.”

Full text public comments without personal health information can be viewed at http://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=255&ExpandComments=n&ver=3&NcaName=Extracorporeal+Photopheresis+(ECP)&DocID=CAG-00324R2&bc=gAAAAAgAIAAA&

**VIII. CMS Analysis**

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1862(l) of the Act).

In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, section 1862(a)(1) of the Social Security Act in part states that, with limited exceptions, no payment may be made under part A or part B for any expenses incurred for items or services:

- Which, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)) or

- In the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section. ((§1862(a)(1)(E)).

Section 1142 of the Social Security Act describes the authority of the AHRQ. Under section 1142, research may be conducted and supported on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically.

Section 1862(a)(1)(E) allows Medicare to cover under coverage with evidence development (CED) certain items or services where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. For your convenience, the 2006 CED guidance document is available at www.cms.gov/determinationprocess/downloads/ced.pdf.

**1862(a)(1)(A)**

**Question**

*Prospectively, do Medicare beneficiaries who have received lung allografts, developed BOS refractory to standard immunosuppressive therapy, and received ECP, experience improved patient-centered health outcomes as indicated by:*

a. *improved forced expiratory volume in one second (FEV1);*
b. *improved survival after transplant; and/or*
c. *improved quality of life?*

In analyzing the evidence, CMS focused on evidence that ECP provides patient-centered health benefits (such as improved survival, less severe BOS, or improved QOL) when used as a second- or third-line treatment of Medicare patients with chronic lung allograft rejection BOS refractory to the usual immunosuppressive therapy regimen.

We note first that the only available evidence is based on conclusions from several retrospective case series. Their limitations as sources of evidence have been acknowledged by their authors. In one article (Benden 2008), the authors commented that, because their study was not a randomized controlled trial (RCT), "unintentional bias may have impacted patient outcome". The decision to commence ECP was at the treating clinician's discretion, leading to the potential for confounding due to variation in treatment. These authors accordingly note that "(d)uring the study period, all recipients were treated with a cyclosporine A-based immunosuppressant regime; however, changes occurred with regards to induction therapy and antiproliferative agents". Finally, the authors acknowledge the small size (n=12) of the group of recipients with BOS treated with ECP. In several ways, the features (and limitations) of the Benden 2008 study are closely comparable to those of the two other studies reviewed below.

In a second article (Morrell 2010), the authors recognized that "(t)his study has some inherent limitations because of the retrospective design. Our study lacked an external control population for comparison. However, individual patients acted as their own controls to assess a spirometric response to ECP, as recommended in the most recent ISHLT update on BOS. The decision to initiate ECP was made on clinical grounds; thus, all eligible patients may not have been treated with ECP. … It is possible that the reduction in the rate of decline after ECP is related to the natural history of BOS itself, rather than the ECP treatment." The authors suggested that a study of FEV1 with a control group of untreated lung allograft recipients with BOS would be both difficult and unethical. The authors commented that the study group experienced a more rapid onset of BOS compared with previously reported data (Trulock 2007), yet the median survival from BOS onset in the study group was "similar to that reported in previous studies" published in the late 1990s. These authors suggested that "(f)urther randomized controlled trials comparing ECP with other immunomodulatory therapies such as cytolytic therapy are necessary to better understand the role and effect of ECP in the management of BOS." Finally, the authors excluded four patients from analysis who died before ECP therapy was complete, but, without further explanation, did not include these patients in their discussion of adverse events during ECP.

The authors of the third retrospective series reviewed for this NCD reconsideration (Villanueva 2000) commented that "(t)his study … was limited by its retrospective design and the small number of patients … It is known that the decline of FEV1 and the survival of patients BOS is variable. Therefore it is possible that the observed effects may be due to chance and not to ECP". They also commented on several other limitations: including lack of randomization and variation in immunosuppressive therapy for individual patients. The authors suggested that further randomized prospective studies should be performed to evaluate the role of ECP in the treatment of BOS. In addition, this article did not include the physiological data (i.e., changes in FEV1 over time) as studied in the Benden 2008 and Morrell 2010 series. This article is more of a descriptive study looking at survival based on BOS classification, using the 1993 ISHLT definitions. For these reasons, this article is not methodologically comparable to the Benden 2008 and Morrell 2010 articles and its findings (other than demographics and adverse events reported) are not further discussed in this analysis.

In summary, the three articles describing outcomes of ECP in patients with BOS after receiving lung allografts may be subject to biases and confounding for several reasons (e.g., selection bias), including those mentioned by their authors. We note in particular variations in individual therapy noted in these articles both prior to and after the onset of BOS. These articles do not provide data separating the effects of these varying therapies from that of ECP are not provided. However, for this national coverage analysis, they contain the only direct evidence available from clinical trials, as confirmed by CMS' internal evidence assessment.

To answer the question above, an ideal clinical study would include a standardized treatment regimen (e.g., indicating in advance a standardized approach to ECP patient selection, frequency, intensity, and duration) and physiological (outcome) assessment methods. Such a study could potentially use a pre-test / post-test design, with each patient serving as their own control. Such designs may help minimize bias and promote uniform data collection and analysis. Lacking the option of an RCT design, other designs which would have been preferred for their greater resistance to potential sources of bias include, for example, prospective clinical trials (including registries) focused on outcomes that indicate benefit relevant to patients. However, such preferable sources of evidence were not available.

CMS notes that other published studies have assessed alternative modalities to avoid BOS progression, e.g., the use of azithromycin to prevent BOS in patients with evidence of acute inflammatory cells (neutrophils) in the bronchioalveolar lavage (Vos 2011), or more aggressive treatment of gastroesophageal reflux to protect bronchial epithelium from damage that may provoke BOS in patients not responsive to azithromycin (Mertens 2011). Because the Morrell 2010 article mentions the use of azithromycin to control BOS, the potential for an interaction between the treatment effects due to azithromycin and those due to ECP exists, and may need to be considered in designing future studies.

Although a number of patients studied were ineligible for Medicare on the grounds of age alone (i.e., they were not 65 years of age or older) an unpublished survey of seven of eight transplant centers by the NCD reconsideration requesters indicated that Medicare beneficiaries account for about 50% of lung transplantation caseload. After transplantation, patients younger than 65 years of age may qualify due to permanent disability status . The median ages of BOS onset in two of the three retrospective case series reviewed are given in the following table (data was not available on the subgroup of twelve patients with BOS treated with ECP in the Benden 2008 study).

| Cited as: | Median Age at BOS Onset |
|---|---|
| Morrell 2010 | 58 years |
| Villanueva 2000 | 48 years |

The data that ECP therapy leads to stabilization or improvement in FEV1 decline in lung allograft recipients with BOS is summarized below. (As noted above, the Villanueva 2000 article did not provide quantitative information on FEV1 decline, using instead BOS severity in its published comparisons.) We note that, in the data about the Medicare cohort tabulated below, mean FEV1 did not improve, but declined at a slower rate. However, the authors of the Morrell 2010 article indicate that a subgroup of 14/56 patients did experience some improvement of FEV1 (mean improvement: 121 mL) following ECP therapy.

| Cited Study: | Mean FEV1 change before ECP therapy | Mean FEV1 change after ECP therapy | Study group size and p value |
|---|---|---|---|
| Benden 2008** | - 112 mL/month | - 12 mL/month | N=12; p = 0.011 |

| | | | |
|---|---|---|---|
| | | | |
| Morrell 2010 | | | |
| - All patients* | - 116.0 mL/month | - 28.9 mL/month | N=56; p < 0.0001 |
| - - Medicare cohort* | - 98.7 mL/month | - 31.9 mL/month | n=25; p = 0.005 |
| - - Non-Medicare* | - 129.9 mL/month | -26.4 mL/month | n=31; p < 0.0001 |

* - comparison in Morrell 2010 is between the mean rate of decline in the six months before ECP treatment and the mean rate of decline in the six months following ECP treatment.
** - comparison in Benden 2008 is between the average FEV1 ‘gradient’ (per month) between the best post-operative (baseline) FEV1 and the FEV1 preceding ECP treatment; the post-ECP average gradient was based on serial FEV1 measurement following completion of twelve cycles of ECP through the last available FEV1 prior to death or the conclusion of the study period, whichever came first.

In summary, based on less preferable retrospective studies as the only available sources of evidence, CMS concludes that the currently available evidence is insufficient to convincingly demonstrate that ECP treatment improves patient-centered health outcomes for Medicare beneficiaries who have developed BOS following lung transplantation. Additional evidence of improvement of patient-centered healthcare outcomes (potentially including studies of improved quality of life in lung allograft recipients due to ECP treatment) would be required for unconditional coverage for ECP therapy in this circumstance. Thus we concluded that ECP for Medicare beneficiaries who have developed BOS following lung transplantation is not reasonable and necessary under 1862(a)(1)(A) of the Act.

**1862(a)(1)(E)**

We believe, based on our review of the available evidence, that CED is an appropriate coverage alternative for ECP for this indication. As explained in the 2006 CED guidance document, cited above, CED facilitates development of additional evidence from approved clinical studies in order to clarify the impact of an item or service on the health outcomes of Medicare beneficiaries. CED enables this additional development of evidence within a research setting where there are added safety, patient protections, monitoring and clinical expertise.

CMS has emphasized these three key conditions governing the appropriateness of a CED coverage determination. The first key condition is that the basic safety of the proposed item or service must be assured. In the case of ECP for this indication, its basic safety has been confirmed by findings from these studies. Adverse events during ECP were noted in ten of 56 patients in the Morrell study. These ten adverse events included eight bacterial line infections, one of which was associated with sepsis and death; one thrombosis distal to the catheter tip, which responded to thrombolytic therapy; and one episode of transient hypotension during ECP, which was treated successfully with a saline fluid bolus. No adverse events were recorded in any of the twelve patients with BOS treated with ECP in the Benden 2008 study. Two of 14 patients in the Villanueva 2000 study suffered line related sepsis that cleared after catheter removal and the use of antibiotic therapy.

This evidence for basic safety of ECP therapy for this indication is summarized in the following table:

| Cited Case Series: | # receiving ECP therapy for BOS | % with ECP-related serious adverse events: |
|---|---|---|
| Benden 2008 | 12 | 0% |
| Morrell 2010 | 56 | 1.78% (sepsis, death) |
| Villanueva 2000 | 14 | 14% (non-fatal sepsis) |

In addition, CMS has indicated that for Medicare beneficiaries who have undergone heart-lung transplantation, ECP is reasonable and necessary for patients with acute cardiac allograft rejection refractory to standard immunosuppressive drug treatment. We believe that this decision speaks to the basic safety of ECP treatment of Medicare allograft recipients. We note also the existing FDA approval for the components of ECP therapy (as indicated above in Section V).

A second key condition for CED is the potential benefit of the proposed item or service to Medicare beneficiaries. For this part of the analysis, the re-analysis of the Morrell 2010 data by the NCD requesters becomes of importance.

In their reanalysis, the NCD requesters compared the monthly rate of decline of FEV1 before and after ECP in both Medicare and non-Medicare patients. They found that this decline was significantly lower following ECP therapy in both groups; that is, there was evidence of a significant change in the rate of decline of FEV1 in the Medicare subgroup:

| Cited Study: | FEV1 decline / 6 months pre-ECP | FEV1 decline / 6 months post-ECP | Study group size and p value |
|---|---|---|---|

| | | | |
|---|---|---|---|
| | | | |
| Morrell 2010 | | | |
| - Medicare | - 98.7 mL/month | - 31.9 mL/month | n=25; p = 0.005 |
| - Non-Medicare | - 129.9 mL/month | -26.4 mL/month | n=31; p < 0.0001 |

CMS notes that the need for evidence that a slowing of the rate of decline in FEV1 has the potential for positive impact on patient quality of life. However, rate of FEV1 decline has been associated with mortality among patients with non-transplant related lung conditions including COPD (for example, Ketelaars 1996). CMS believes that a lower rate of FEV1 decline has not yet been associated with improvement in any other measurable health outcome and encourages further research into this question.

The third key condition for CED is difficulty in conducting clinical studies. CMS is aware that clinical studies of ECP for this indication may be more difficult to perform due to the limited number of Medicare beneficiaries who would not only be clinically eligible but also would prospectively agree to participate in such studies. An indication of the difficulty of such trials is the relative lack of current research efforts listed on http://www.clinicaltrials.gov for the search terms 'ECP' and 'bronchiolitis obliterans'. One such study, entitled "Extracorporeal Photopheresis in Patients With Bronchiolitis Obliterans Syndrome (BOS) After Lung Transplantation" (clinicaltrials.gov identifier: NCT00502554) was described (as of October 27, 2011) as 'Terminated' with the explanation "insufficient patient recruitment and ECP capacity".

We also note the public comment of ASFA, which mentioned the difficulty of conducting such trials. However, CMS believes that a clinical trial including qualifying patients from multiple transplant centers could overcome this difficulty. We also recognize that other study designs (other than randomized controlled trials) may be appropriate to address the research questions above.

CMS proposes that based on the available evidence, ECP for this indication fulfills the criteria for CED coverage.

**Health Disparities**

A review of articles discussed above in this decision memorandum reveals no analysis of ECP clinical outcome by racial or ethnic categories. Any inference about relative benefits of ECP for control of BOS among lung transplantation recipients in specific racial or ethnic groups would be, at best, speculative. CMS also notes the absence of evidence about benefits or harms related to other population classifiers that have been associated historically with healthcare access or outcome disparities, such as gender, sexual orientation, religion, and age, and encourages additional studies in which such associations might be studied.

However, there is some information about disparity in overall survival among lung transplant recipients. In a large retrospective cohort study, based on 16,875 adults who received primary lung transplants from 1987 to 2009 according to the Uniform Network for Organ Sharing (UNOS) database, Liu et al., 2011 examined the risk of death after lung transplant for nonwhites compared with that for whites using time-to-event analysis. The percentage of nonwhite transplant recipients increased from 8.8% (before 1996) to 15.0% (2005-2009). In the modern transplant era (2001-2009), survival improved for all patients. However, a greater improvement among nonwhites has eliminated the disparities in survival between the races (5-year survival, 52.5% vs. 51.6%). The authors concluded that, in contrast to the period 1987-2000, there was no significant difference in lung transplant survival between whites and nonwhites in the period 2001-2009. The authors commented that advances in surgical technique or immunosuppressant therapy might account for this change. However, this study did not collect data on incidence of BOS; causes of death among study subjects; or exposure to ECP therapy for the various racial and ethnic subgroups.

This lack of evidence about racial and ethnic factors and the response to ECP treatment represents in our view an evidence gap which we encourage trial designers to consider when proposing clinical trial designs for ECP under this NCD. While recognizing that this consideration may complicate the design of appropriate clinical studies, we will nevertheless prefer clinical study proposals in which data on racial and ethnic factors are specifically collected and analyzed.

**Duration of CED coverage for ECP for this indication**

CMS considers the results of all CED clinical studies critical in the evolution of medical technology and in the evaluation of the benefit of items and services covered under CED. Because of this, CMS does not consider an NCD that requires CED as a condition of payment to be a permanent policy. In past, CMS has not put time limitations on NCDs that require enrollment in clinical studies for coverage. This has lead to a number of circumstances that may have been avoided by establishing time limits, including having a standing NCD without any CED clinical studies being conducted and allowing payment for studies that have never produced evidence. CMS proposes setting specific time limits for future CED NCDs, including this one.

We propose a two stage expiration process for this CED decision. In the first stage, we will require that all clinical studies under which there is CED coverage for ECP for BOS must be approved within two years of the date on which this final NCD is issued. If there are no approved clinical studies on that date, this NCD will expire and coverage of ECP for BOS will revert to the coverage policy in effect prior to the issuance of this NCD. We base this proposed time period on CMS' experience with earlier CED decisions in which approvals for CED clinical trials have been completed within several months after the NCD date.

If there is at least one approved clinical study, we will proceed to the second stage. For each approved study of ECP for BOS, we will establish a specific time period during which ECP will be covered under this NCD. We will allow enough time, based on the study protocol, for the expected number of patients to be enrolled and for the treatment to be administered to the last patient in the study. After that, coverage for ECP for BOS for the particular clinical study will no longer be available. The time period will be based on the following factors:

1. The study design;
2. The expected sample size needed to obtain a statistically significant effect size, and
3. The expected enrollment rate, which is based on the prevalence of the condition in the population, the mechanism of action of the treatment, and the duration of treatment.

Recognizing that this proposed method for estimating the appropriate sunset interval for a coverage decision should be subject to public review and comment, CMS welcomes comments or suggestions on the technique of calculating an appropriate sunset time for CED -supported studies.

**Summary:**

CMS proposes that the evidence is insufficient to conclude that, in Medicare beneficiaries with BOS developing after lung allograft transplantation refractory to standard immunosuppressive therapy, ECP will improve patient centered health outcomes. However, based on its previously published criteria for considering CED, CMS concludes that evidence of basic safety, potential for patient-centered health outcome improvement, and demonstrated difficulty of conducting appropriate clinical trials, are sufficient in combination to persuade CMS to propose this form of coverage for ECP therapy for BOS after lung allograft transplantation.

As noted above, an ideal clinical study would include a standardized treatment regimen (e.g., indicating in advance a standardized approach to ECP patient selection, frequency, intensity, and duration) and physiological (outcome) assessment methods. Such a study could potentially use a pre-test / post-test design, with each patient serving as their own control. Such designs may help minimize bias and promote uniform data collection and analysis. Lacking the option of an RCT design, other designs which would have been preferred for their greater resistance to potential sources of bias include, for example, prospective clinical trials (including registries) focused on outcomes that indicate benefit relevant to patients.

CMS further proposes that any applications for coverage of ECP in CED studies for this indication pursuant to this NCD must be received and approved by May 2, 2014. If there are no approved clinical studies on this date, this NCD will expire and coverage of ECP for BOS will revert to the coverage policy in effect prior to the issuance of the final DM for this NCD.

CMS also notes that no evidence from this proposed decision memorandum supports any modification of existing coverage status of ECP used for other indications (e.g., for cutaneous T-cell lymphoma).

## IX. Conclusion

The Centers for Medicare & Medicaid Services (CMS) proposes that the available evidence is insufficient to conclude that extracorporeal photopheresis (ECP) improves beneficiary health outcomes as second-line therapy for Medicare beneficiaries who are recipients of lung allografts and who have developed bronchiolitis obliterans syndrome (BOS) refractory to standard immunosuppressive therapy. We therefore propose that coverage for ECP for this indication is not reasonable and necessary under §1862 (a) (1) (A) of the Social Security Act (hereinafter 'the Act').

However, we believe that ECP may, upon development of additional evidence, prove to represent a substantial benefit to Medicare beneficiaries who are recipients of lung transplants and who have developed BOS refractory to standard immunosuppressive therapy. CMS review of clinical trials confirms not only the basic safety of ECP therapy but also the difficulty of conducting clinical trials. Therefore, CMS proposes that ECP for this indication be approved under Coverage with Evidence Development (CED).

Accordingly, CMS proposes coverage for ECP for this indication only when ECP is provided under a clinical research study that meets the following conditions.

The clinical research study meets the requirements specified below to assess the effect of ECP for the treatment of BOS following lung allograft transplantation. The clinical study must address one or more aspects of the following question:

Prospectively, do Medicare beneficiaries who have received lung allografts, developed BOS refractory to standard immunosuppressive therapy, and received ECP, experience improved patient-centered health outcomes as indicated by:

a. improved forced expiratory volume in one second (FEV1);
b. improved survival after transplant; and/or
c. improved quality of life?

We note for the sake of clarification of terms that certain sections of this document refer to an existing international classification of the severity of BOS, the 2002 International Society for Heart and Lung Transplantation (ISHLT) definition of BOS (please see table, p. 5). In one area below, we refer to an earlier (1993) version of this classification used by the Villanueva 2000 study (please see p. 12 below), one clinical study germane to this decision.

This decision would not modify existing requirements for any other covered or non-covered indication for ECP (Section 110.4 Medicare National Coverage Determinations Manual).

The required clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether ECP potentially improves the participants' health outcomes.
b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR parts 50 and 56.
g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors

   (http://www.icmje.org).
l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

CMS further proposes that any applications for coverage of ECP in CED studies for this indication pursuant to this NCD must be received and approved by May 2, 2014. If there are no approved clinical studies on this date, this NCD will expire and coverage of ECP for BOS will revert to the coverage policy in effect prior to the issuance of the final DM for this NCD.

In order to maintain an open and transparent process, we are seeking comments on our proposal. We will respond to public comments in a final decision memorandum, consistent with the spirit of §1862(l) (3) of the Act.

## APPENDIX A

### General Methodological Principles of Study Design

(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

**Assessing Individual Studies**

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

**Generalizability of Clinical Evidence to the Medicare Population**

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

**Assessing the Relative Magnitude of Risks and Benefits**

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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